PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatable but not curable cancer in England: a retrospective cohort study using cancer registry data and linked datasets.
AUTHORS	Stanley, Fintan; White, Rachel; Than, Jen; Macnair, Archie; Pethick, Joanna; Fallica, Gregory; Hounsome, Luke; Maher, J

VERSION 1 – REVIEW

REVIEWER	Elizabeth Sarma National Cancer Institute, USA
REVIEW RETURNED	15-Jun-2020

GENERAL COMMENTS	This study aimed to use English cancer registry data to quantify the population living with treatable but not curable (TbnC) cancer. Though the general idea of quantifying these cases is appealing, I had difficulty following the logic used by the authors to justify the need to quantify these cases and their methodology. Since TbnC cases represent such a heterogeneous group, what value is this categorization? How will it help in planning support services? I am not clear on how this label is going to be useful in personalizing cancer care. In addition, though I understand the advantage of using registry data, there is still a great deal of subjectivity in the definition formation. The manuscript demands much of readers to decipher the process used to arrive at the 12 criteria, and to understand the criteria and how they were used to quantify cases. A much stronger case must be made for the importance of labeling these cases in this manner and the author's selected approach to this labeling.

REVIEWER	Eloise Radcliffe University of Southampton, UK I am employed as a Research Fellow at the University of Southampton on a study funded by Macmillan Cancer Support.
REVIEW RETURNED	16-Jun-2020

GENERAL COMMENTS	This is an important and original piece of work to define and quantify an under-recognised population living with treatable but not curable cancer. It is clear that a great deal of work has gone into this analysis and the findings have important implications for clinical practise. The paper is generally well-structured and well-written however more detail and clarification in places would strengthen the paper, particularly on the work that went into the development of the definition. The abstract and strengths and limitations are clear and well-written.

	Introduction - This provides a clear objective and a good justification for the study. In paragraph 2 the phrase “”safety net’ support” is used- please specify what this refers to and/ or give examples. The paper by McConnell, White and Maher (2017) is referenced- it would be helpful to have more detail on the ‘intermediate survival group’ (ie how long?) and how this relates to the TbnC group. Methods- More detail in the ‘Definition Development’ section would strengthen the paper. More information is needed on the interviews with stakeholders, people living with TbnC, and the consultations with healthcare professionals and academics and the analysis of how people living with cancer describe their condition on social media. It is clear that a lot of work has gone into developing the definition but unfortunately this is glossed over and much more detail needs to be given on the methods for the interviews, the sample (ie who was interviewed and where were they were recruited from etc), the type of analysis of social media. Also please give details of how each of these pieces of work fed into the definition. If necessary, put more information in an appendix but more detail needs to be added into the main body of the paper to demonstrate the robustness of the definition. Patient and Public Involvement- It is stated that patients were involved in the development of the TbnC terminology. It is unclear if this refers to the patient interviews mentioned in the ‘Definition Development’ section. Earlier on (perhaps in the introduction) it would be helpful please clarify the difference or the relation between the definition of ‘advanced cancer’ and ‘treatable but not curable cancer’, particularly as papers that are referenced in the introduction and in the discussion in the ‘Relation to other studies’ section) refer to ‘advanced cancer’. There are a few acronyms that are not given in full the first time they are written (eg. SACT, NCRAS, STROBE, EoL) Figure 1- I like the visual representation of the study flow but it is not clear whether it includes the development of the TbnC definition. If so, it should also include input from patient interviews, stakeholders etc and the analysis of how people living with cancer describe their condition on social media. In this figure there is the first mention of ‘expert groups’ who were consulted thoughout the study- this needs to be in the main body of the text. Is this different to the ‘consultations with healthcare professionals and academics’ mentioned in the ‘Definition Development’ section? These consultations sounded like a one-off rather than something that was continuous throughout the study, please clarify. Referencing- this needs to be in a different style- each reference should only be listed once.

REVIEWER	Peter Baade Cancer Council Queensland Australia

REVIEW RETURNED	16-Jul-2020

GENERAL COMMENTS	This is a generally well-written study that seeks to estimate the prevalence of cancers which are categorised as treatable but not curable (TbnC) based on data in the cancer registry in England. The study represents an impressive and sizeable body of work, involving extensive consultation with stakeholders during the development of the criteria. I could find no statement about ethics in the manuscript, either for the various interviews and workshops with stakeholders or the data linkages. I do have some specific comments below that may help in further refining and improving the manuscript. Please note that page numbers in these comments refer to the document pages (top of screen) not the numbers at the bottom of the page. Page 3. Line 9. The term “search criteria” seems (to me) to suggest carrying out a literature review. In contrast the methodology described here could better be described as a numerical algorithm to categorise cancer cases into different groups. Page 7. Please provide details of which linked databases were used, even if just their names. The abstract mentions 5 data sets. Are these databases linked deterministically? Also, the title suggests this is using cancer registry data only – I would suggest changing this to refer to linked datasets. Page 7. The label “Group B” is very non-informative. Can a more descriptive label be used? Page 9. The second “Prevalence” should be “Occurrence”. Page 9. Occurrence (the second prevalence). Given that meeting the same criteria more than once only counts as one, suggest revising the definition as “number of times a distinct TbnC criteria was met” Page 9. Under incidence, rather than “not anytime previously” – given only a three year window is considered, I would suggest specifically stated “and not previously during 2012-2014”. Page 11. The jumping between including and excluding the EoL category gets confusing. In addition, while the categories for TbnC can be calculated and defined prospectively, EoL can only be defined retrospectively. Thus whether a person is TbnC or EoL cannot be determined until after the person has died. For this reason I wasn’t sure how relevant it was to split the two, particularly if there is any intent to identify these groups prospectively, given the authors state that they require “personalised treatment and support”. Page 11. Most of the results are reported as numbers and percentages, which is appropriate. The statistics presented in lines 4-7 need some detail (in the methods) about what they are and how they were calculated. Is the estimate of (2.6 +-1.7) the mean number of criteria met plus or minus the standard deviation? How skewed is the distribution? Is a mean appropriate for a potentially

	highly skewed ordinal scale? I noticed in the STROBE checklist a t-test was used – this should be noted in the manuscript. Page 12, lines 29-35. The two percentages are not directly comparable given the different methodologies and time periods. Is the difference due to the calculation of the estimate, Page 23. Under the Twelve Selection Criteria, the distinction between TbnC and Group B appears to be the subjective decision of the project's clinical working group. How reproducible is this? Does this relate to a case-by-case consideration? Page 23. The first two criteria differentiate between TbnC and Group B. This is not the case for most of the other criteria. Are all cases initially assumed to be TbnC, and then any satisfying Group B criteria (based on #1 and #2 for example) they are recoded as Group B? Was a similar process undertaken for the EoL group (that is, the EoL cases are extracted from the broader group)?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 Comments

This study aimed to use English cancer registry data to quantify the population living with treatable but not curable (TbnC) cancer. Though the general idea of quantifying these cases is appealing, I had difficulty following the logic used by the authors to justify the need to quantify these cases and their methodology. Since TbnC cases represent such a heterogeneous group, what value is this categorization? How will it help in planning support services? I am not clear on how this label is going to be useful in personalizing cancer care. In addition, though I understand the advantage of using registry data, there is still a great deal of subjectivity in the definition formation. The manuscript demands much of readers to decipher the process used to arrive at the 12 criteria, and to understand the criteria and how they were used to quantify cases. A much stronger case must be made for the importance of labelling these cases in this manner and the author's selected approach to this labelling.

Thank you for your feedback.

We have added to the description that the TbnC population is heterogeneous. However, this heterogeneity does not make the TbnC concept of lower value. People living with TbnC cancer can be poorly served by cancer services as these tend to focus on either end of life care or aiming to eradicated disease. As highlighted in the introduction they require personalised practical and emotional support with uncertainty and complex cancer journeys. To provide this support on a national scale requires policy makers and service providers to acknowledge this group.

We have expanded our explanation of why quantifying the population is key to providing support for the TbnC population. The first step to making the case for providing the support is to quantify the population; for many policy makers and service providers 'it doesn't count if you don't count it'. Quantifying the population demonstrates the size of the issue, helps to gauge the magnitude of the needs, provides credibility and provides a baseline for trend analysis to help anticipate changes in the population.

We acknowledge there that this is not a widely used terminology, yet, but there are related terms, like 'advanced' or 'terminal' that are used broadly but we believe without clear definitions and lacking the

transparency in Treatable but not Curable. Other terms also often associated with death rather than potentially many years of living with cancer. As described in our methods section TbnC was developed through extensive research and found to be meaningful, acceptable to people living with cancer and professionals and useful in practice.

Using registry data has been a key strength of this project as it has allowed us to include all people living with cancer in England within the analysis. This population level view is essential for national influencing to support the TbnC population. The other key advantage of registry data is that it is linked to many other person level datasets such as Hospital Episode Statistics and the results of the National Cancer Patient Experience Survey. This linkage makes it possible for further work to analyse the population and explore there needs and experiences so that future services can be tailored to their needs.

We have added additional information (especially to the strengths and limitations section) to highlight that the algorithm is derived from clinical opinions and the challenge in building a set of rules that work for all the diversity of people living with cancer. Marginal cases and subjectivity are unavoidable in this kind of work, but we do not believe this decreases the value of the work – “all models are wrong, but some are useful”.

We are sorry to hear that the manuscript required deciphering - it was a complicated iterative process that we have perhaps struggled to wholly illustrate within the constraints of the article format. Again, informed by the feedback from the editors and peer-reviewers we have made changes throughout the manuscript that we hope better to communicate our objectives, justifications and methods.

Reviewer #2 Comments

This is an important and original piece of work to define and quantify an under-recognised population living with treatable but not curable cancer. It is clear that a great deal of work has gone into this analysis and the findings have important implications for clinical practise. The paper is generally well-structured and well-written however more detail and clarification in places would strengthen the paper, particularly on the work that went into the development of the definition. The abstract and strengths and limitations are clear and well-written. Introduction - This provides a clear objective and a good justification for the study.

1. In paragraph 2 the phrase “”safety net’ support” is used- please specify what this refers to and/ or give examples.

   We have added a statement to summarise the kinds of services and support we were referring to here.

2. The paper by McConnell, White and Maher (2017) is referenced- it would be helpful to have more detail on the ‘intermediate survival group’ (i.e. how long?) and how this relates to the TbnC group.

   We have added more specific detail from this study to the intro and discussion as that study was an important precursor to this one.

3. Methods- More detail in the ‘Definition Development’ section would strengthen the paper. More information is needed on the interviews with stakeholders, people living with TbnC, and the consultations with healthcare professionals and academics and the analysis of how people living with cancer describe their condition on social media. It is clear that a lot of work has gone into developing the definition but unfortunately this is glossed over and much more detail needs to be given on the methods for the interviews, the sample (i.e. who was interviewed and where were they were recruited from etc), the type of analysis of social media. Also please give details of how each of these pieces of work fed into the definition. If necessary, put more information in an appendix but more detail needs to be added into the main body of the paper to demonstrate the robustness of the definition.

   The study focuses on the quantification of the TbnC cohort, but we recognise that defining the group is relevant and import information. We have expanded the methods section relating to the concept development, providing more, but not exhaustive detail. We have also separated out this work from the data flow chart so that the process development and data flow are represented separately in figure 1 & 2. In reality the processes informed each other but hopefully these additions address any ambiguity and offer a sufficient and clear account of both aspects of the methods.

4. Patient and Public Involvement- It is stated that patients were involved in the development of the TbnC terminology. It is unclear if this refers to the patient interviews mentioned in the ‘Definition Development’ section.

   Patients were only directly involved in the earliest stage when the specific phrasing Treatable but not Curable was being developed. They were not involved in later stage where the stakeholder groups consisted of clinical experts and data specialists. We have tried to clarify this in the text. Further patient and public involvement would have been ideal but to

meaningfully involve people living with TbnC with the necessary sensitivity around this issue within the analysis stages of the project was not possible within the timescales of the project.

5. Earlier on (perhaps in the introduction) it would be helpful please clarify the difference or the relation between the definition of ‘advanced cancer’ and ‘treatable but not curable cancer’, particularly as papers that are referenced in the introduction and in the discussion in the ‘Relation to other studies’ section) refer to ‘advanced cancer’.

   It is difficult to draw clear line of comparison between these, and other terms that relate to the TbnC cohort. For example, terms like advanced cancer are not used consistently in the literature and apply differently across cancer types especially the homological cancers. This was a major motivation in our work here, to arrive at a detailed algorithm that provides a consistent and transparent definition. We added details to the intro and discussion (relation to other studies) to try to tackle this point directly.

6. There are a few acronyms that are not given in full the first time they are written (e.g. SACT, NCRAS, STROBE, EoL)

   Sorry for this oversight, we have added in these definitions.

7. Figure 1- I like the visual representation of the study flow but it is not clear whether it includes the development of the TbnC definition. If so, it should also include input from patient interviews, stakeholders etc and the analysis of how people living with cancer describe their condition on social media. In this figure there is the first mention of ‘expert groups’ who were consulted throughout the study- this needs to be in the main body of the text. Is this different to the ‘consultations with healthcare professionals and academics’ mentioned in the ‘Definition Development’ section? These consultations sounded like a one-off rather than something that was continuous throughout the study, please clarify.

   Figure 1 only refers to the process covered in the Algorithm Development of the text. The work with ‘expert groups’ in question were referred to as workshops, we have added to this section in the document to clarify.

8. Referencing- this needs to be in a different style- each reference should only be listed once.

   Apologies, we have re-written the references and bibliography to correct this error.

Reviewer #3 Comments

This is a generally well-written study that seeks to estimate the prevalence of cancers which are categorised as treatable but not curable (TbnC) based on data in the cancer registry in England. The study represents an impressive and sizeable body of work, involving extensive consultation with stakeholders during the development of the criteria.

1. I could find no statement about ethics in the manuscript, either for the various interviews and workshops with stakeholders or the data linkages.

   We have included details of the legal basis for our access to the patient data, which allows this analysis without requiring specific additional ethical approval.

I do have some specific comments below that may help in further refining and improving the manuscript. Please note that page numbers in these comments refer to the document pages (top of screen) not the numbers at the bottom of the page.

2. Page 3. Line 9. The term “search criteria” seems (to me) to suggest carrying out a literature review. In contrast the methodology described here could better be described as a numerical algorithm to categorise cancer cases into different groups.

   We have revised the wording to highlight the algorithmic nature of the code used in the analysis, but we do at times still use the term search criteria to refer to the induvial branches of the algorithm that map to related data fields and specific clinical contexts.

3. Page 7. Please provide details of which linked databases were used, even if just their names. The abstract mentions 5 data sets. Are these databases linked deterministically? Also, the title suggests this is using cancer registry data only – I would suggest changing this to refer to linked datasets.

   Linkage was not designed by the authors and is a detailed process that would be a whole (worthy) article in itself, we have however given additional detail on the datasets and pointed readers to more information on them and their linkage through referencing.

4. Page 7. The label “Group B” is very non-informative. Can a more descriptive label be used?

   We report on Group B as many of the clinical stakeholder believed in the importance of this group’s consideration. Future work to look at how Group B experience is similar or different to TbnC will need to be carried out before additional work with patients and advocates around transparent terminology. There was a process around arriving at the TbnC definition and we think it best we follow the same process for group B. And while we recognise that would be related to this study, and indeed likely dependant on the reception of this study, we still see it as future and distinct work.

   In effect the distinction between the two was not an expected outcome of our study. So, for now we have offered an early report under a preliminary label.

5. Page 9. The second “Prevalence” should be “Occurrence”.

   Yes, it should be.

6. Page 9. Occurrence (the second prevalence). Given that meeting the same criteria more than once only counts as one, suggest revising the definition as “number of times a distinct TbnC criteria was met”

   We have changed this, thank you for offering a clearer wording.

7. Page 9. Under incidence, rather than “not anytime previously” – given only a three-year window is considered, I would suggest specifically stated “and not previously during 2012-2014”.

   We made the suggested change and agree it’s more transparent.

8. Page 11. The jumping between including and excluding the EoL category gets confusing. In addition, while the categories for TbnC can be calculated and defined prospectively, EoL can only be defined retrospectively. Thus, whether a person is TbnC or EoL cannot be determined until after the person has died. For this reason, I wasn’t sure how relevant it was to split the

two, particularly if there is any intent to identify these groups prospectively, given the authors state that they require “personalised treatment and support”.

We have restructured the indicated section to separate out the information on people in there last year of life. Hopefully this increases the sections readability.

Clinicians need to tailor support based on their best predictions of how long someone is likely to have left. Someone with only days or weeks to live requires differences in care to someone who is TbnC, this reality is the main reason we see these groups as distinct. However, there is very little information in the cancer registry or linked datasets to describe this transition to end of life care and needs. The only consistent measure available in the national datasets is vital status and so this was used to create an assumption-based time period of a year. Using this method has the advantage that it has been used in other research and can be applied consistently. We have presented the numbers in their last year of life to aid in understanding of the impact of this one-year assumption.

The algorithm we have built is designed to be applied to the cancer registry and linked databases to predict who is likely to be living with TbnC. This will be used for population level analysis to design services that provide personal support and launch conversations rather than to identify the support needs of individual people living with cancer. This study will help lay the foundations for identifying people living with TbnC cancer prospectively. However, further work will be needed to incorporate the far more detailed and nuanced information clinicians hold about individual patients.

9. Page 11. Most of the results are reported as numbers and percentages, which is appropriate. The statistics presented in lines 4-7 need some detail (in the methods) about what they are and how they were calculated. Is the estimate of (2.6 +-1.7) the mean number of criteria met plus or minus the standard deviation? How skewed is the distribution? Is a mean appropriate for a potentially highly skewed ordinal scale? I noticed in the STROBE checklist a t-test was used – this should be noted in the manuscript.

   We believe the use of the t-test is still valid, despite concerns of the skewed distribution, due to the large group sizes (central limit theorem) and had presented this as arithmetic means are easily understood. However, we can see the concern and had considered alternatives. Now presented is a t-test run on **ln** transformed data to directly address issues from the distribution of the underlying data. We have added details of the tests in the methods section and in text we opted to report median and ranges.

10. Page 12, lines 29-35. The two percentages are not directly comparable given the different methodologies and time periods. Is the difference due to the calculation of the estimate?

    We agree there is difficulty comparing studies where definitions don’t map to each other. This was in fact and underlying motivation of this work, to offer a transparent definition to be tested and shared. However, offering comparisons to other work in the context still felt important, we have added statements to that sections to better communicate this.

11. Page 23. Under the Twelve Selection Criteria, the distinction between TbnC and Group B appears to be the subjective decision of the project’s clinical working group. How reproducible is this? Does this relate to a case-by-case consideration?

    We acknowledge the subjectivity of the clinical input in our opening Strengths and Limitations section. The distinction was shaped by 5-year survival rate data, and clinical expertise. The

differences between someone living with stage 4 breast cancer and stage 2 pancreatic cancer were extensively discussed. Both have a high chance of dying due to their cancer however, the early stage pancreatic cancer is less clearly 'not curable'. These differences are part of the reality of cancer care and so we believe are likely to come out in a repeat of the discussions.

Perhaps in time the data quality and time ranges will allow for a more data-based designation, but for now we offer one based on the admittedly subjective professional opinions. We acknowledge and contend with some of the weakness arising from subjective calls and marginal cases in the Strengths and Weaknesses section of our Discussion.

12. Page 23. The first two criteria differentiate between TbnC and Group B. This is not the case for most of the other criteria. Are all cases initially assumed to be TbnC, and then any satisfying Group B criteria (based on #1 and #2 for example) they are recoded as Group B? Was a similar process undertaken for the EoL group (that is, the EoL cases are extracted from the broader group)?

    If someone meets the criteria for both TbnC and Group B we have classified them into TbnC. For example, if someone has a group B cancer such as stage 2 lung cancer and then meets a TbnC criteria such as receiving palliative intent treatment it is likely that at the index date their cancer has progressed, so they are now living with TbnC cancer. Once someone meets the criteria for TbnC it is assumed to be life long and so they can not go back to being in Group B.

    End of life (EoL) status is only assessed for those who meet the criteria for TbnC or Group B. It does not include those who died without meeting either the TbnC or Group B criteria. Based on our definition of TbnC, EoL status has priority so all those who die within 2016 are included.

    TbnC status is defined exhaustively first, if there is evidence that would indicate Group B this does **not** supersede TbnC status. For Prevalence counts Group B designation only occurs when there is an indication for it and no co-existing data indicating TbnC. End of Life status is tagged to all records, event or patient level. Results are then shared based on separating these groups. We have added details to the methods section to clarify this.

VERSION 2 – REVIEW

REVIEWER	Eloise Radcliffe University of Southampton UK I am employed as a Research Fellow at the University of Southampton on a study funded by Macmillan Cancer Support
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	Thank you for your revisions. I feel you have adequately addressed my comments and the paper has really been strengthened, particularly the introduction and methods. This is an important and original piece of work to define and quantify an under-recognised population living with cancer that is treatable but not curable and I recommend that the paper is accepted for publication. I have only a few minor comments below. I recognise that this paper focuses on the quantification of TbnC cases and there is a word-limit but I think a bit more clarification on the development of the definition would be helpful (see below).

	Page 4: Please clarify the meaning of ‘edge case’ P5: ‘Safety net’ support’ should also include psychological support. Methods section p7: The following sentence is incomplete: ‘Additional in dept structured interviews(n=11) with people living with TbnC cancer.’ Could you add a sentence or two after the sentence below to clarify what kind of analysis was carried out on online cancer support forums and what kind of review of the published evidence was carried out (eg. systematic/ scoping etc). ‘The term was further tested through secondary analysis of the afore mentioned work, analysis of online cancer support forums, and review of the available published evidence.’ Write ‘PWLC’ in full.

REVIEWER	Peter Baade Cancer Council Queensland
REVIEW RETURNED	28-Oct-2020

GENERAL COMMENTS	Thanks for your thoughtful consideration of each of the points raised, and the steps you have taken to address them.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2 Comments

Thank you for your revisions. I feel you have adequately addressed my comments and the paper has really been strengthened, particularly the introduction and methods. This is an important and original piece of work to define and quantify an under-recognised population living with cancer that is treatable but not curable and I recommend that the paper is accepted for publication.

We agree the revisions have strengthened the piece and so thank you for the time you’ve given to review our work.

I have only a few minor comments below. I recognise that this paper focuses on the quantification of TbnC cases and there is a word-limit but I think a bit more clarification on the development of the definition would be helpful (see below).

Page 4: Please clarify the meaning of ‘edge case’

We have revised this to wording to “marginal cases”, as this is the wording used elsewhere (methods and discussion) to discuss cases that might be challenging to decide to include or exclude from the TbnC concept definition, though they are caught within the algorithms definition.

P5: ‘Safety net’ support’ should also include psychological support.

Yes, it should, we have added this, thank you.

Methods section p7: The following sentence is incomplete:
‘Additional in dept structured interviews(n=11) with people living with TbnC cancer.’

We have given this sentence the ending that it probably deserved.

Could you add a sentence or two after the sentence to clarify what kind of analysis was carried out on online cancer support forums and what kind of review of the published evidence was carried out (eg. systematic/ scoping etc).

We have added some detail to this section to mention the approaches taken in the forum analysis and literature review.

Write ‘PWLC’ in full.

We’ve written out the term in full.

Reviewer #3 Comments

Thanks for your thoughtful consideration of each of the points raised, and the steps you have taken to address them.

Thank you for the time you’ve given to review our work.